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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,863	01/15/2004	Leonard Presta	P1726R1D1	5958

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EXAMINER	
CROWDER, CHUN	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,863	PRESTA, LEONARD	
	Examiner	Art Unit	
	Chun Crowder	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/20/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 20, 2007, has been entered.

2. Applicant's amendment to the claims, filed April 20, 2007, has been entered.

Claims 1-18 have been previously canceled.
Claims 19 and 20 have been amended.
Claims 21 have been added.

Claims 19-21 are currently pending and under consideration as they read on the originally elected invention of a method for treating lymphoma or leukemia by administering an variant anti-CD20 antibody comprising substitutions at positions 298, 333, and 334 in the Fc region.

3. This Office Action is in response to Applicant's amendment to the claims and remarks filed April 20, 2007.

The rejections of record can be found in the previous Office Actions, mailed on October 11, 2005 and May 22, 2006.

4. Applicant's IDS, filed on April 20, 2007, has been considered.

5. Upon reconsideration as well as applicant's argument, the previous rejection under 35 U.S.C. 112, first paragraph has been withdrawn.

6. This is a **New Ground of Rejection**. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20-21 are indefinite in that they only describe the number of amino acid residue positions without reciting the numbering system.

It is suggested to amend the claim to recite the particular numbering system used (e.g. EU numbering system).

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

8. This is a **New Ground of Rejection**. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim19-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating lymphoma by administering a variant anti-CD20 antibody and comprises an Fc region which mediates ADCC more effectively than the parent antibody and comprises amino acid modification in the Fc region selected from positions 298, 333, and 334, does not reasonably provide enablement for said method by administering a variant anti-CD20 antibody comprising "at least one amino acid modification in the Fc region" and/or "one or more amino acid substitutions" in the Fc region and for treating any leukemia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 19-21 are drawn to a method for treating lymphoma or leukemia n a mammal comprising administering to the mammal a therapeutically effective amount of a variant of a parent antibody which binds CD20 and comprises an Fc region, which variant mediates ADCC in the presence of human effector cells more effectively than the parent antibody and comprises at least one amino acid and/or one or more amino acid substitution in the Fc region.

The specification discloses that certain substitutions in amino acid residues in Fc region of IgG antibody can improve binding affinities to the Fc receptors and improve ADCC (e.g. see Example 4 on pages 70-85). The specification further discloses certain combination mutations in the Fc region [e.g. S317A/K353A (298 and 334 in EU numbering)] bind FcγRIIIA better than wild type Fc as disclosed in Figure 14 and page 10 of the instant specification).

However, the specification does not provide a sufficient enabling description of the claimed invention. The disclosure appears to show only antibodies with certain specified amino acid substitutions and certain combination mutations in the Fc region for improved binding to Fc receptors and/or improved ADCC. The instant claims encompass in their breadth *any* anti-CD20 antibody comprising a Fc variant comprising at least one amino acid modification in the Fc region and/or combinations mutations without setting forth the positions of those amino acid modifications.

However, there does not appear to be sufficient guidance in the specification as field as to how the skilled artisan would make and use the claimed anti-CD20 antibody encompassing a variant Fc region comprising at elast one amino acid modification in the Fc region and/or one or more amino acid substitutions, wherein said antibody mediates ADCC more effectively than the parent antibody. The state of the art at the time the invention was made recognized that even single amino acid differences can result in drastically altered function of antibodies. For example, Lund et al. (The Journal of Immunology 1996, 157:4963-4969, reference 102 on IDS filed on October 11, 2005) show that even a single amino acid replacement within the CH2 domain of IgG can alter the glycosylation profile of an antibody therefore influence its effector functions of Fc receptor binding and complement activation (see entire document, particularly Discussion on pages 4966-4968).

Given the extensive variation permitted by the instant claim language, the skilled artisan would not reasonably predict such anti-CD20 antibody encompassing a variant Fc region comprising at least one amino acid modification in the Fc region and/or one or more amino acid substitutions to have the same function as the instant claimed invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. This is a **New Ground of Rejection**. Claim 19 is rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al. (US Patent 5,736,137, reference 10 on IDS filed on October 11, 2005) (see entire document) in view of the alignment of native sequence of IgG Fc regions in Figure 22A of the instant specification.

Anderson et al. teach a method for treating human B cell lymphoma using chimeric anti-CD20 antibody that comprises human IgG1 Fc region (see entire document, particularly Figure 1 and columns 7-8). Anderson et al. further teach that the chimeric antibody mediates ADCC more effectively than the murine anti-CD20 antibody (e.g. see columns 19-20, in particular).

As evidenced by the instant specification, the Fc region of human IgG1 and murine IgG1 is highly homologous and differ only in few amino acid residues (see Figure 22 of the instant specification, in particularly); thus, human Fc is read as variant of murine Fc comprising at least one amino acid modification in the Fc region.

Given that the "parent antibody" is defined as a polypeptide comprising an amino acid sequence which lacks one or more modification in the Fc region (e.g. see page 12 of the instant specification), the murine anti-CD20 antibody taught by Anderson et al. is read as the parent antibody comprising an Fc region that lacks amino acid modification in the Fc region and the chimeric anti-CD20 antibody comprising human Fc region is interpretated as the variant antibody comprising at least one or more amino acid modification in the Fc region.

Therefore, the reference teachings anticipate the claimed invention.

12. Claims 19, 20 and newly added claim 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Idusogie et al. (US Patent 6,528,624, claims priority to provisional USSN 60/080,447 filed on April 2, 1998. Reference 16 on IDS filed on October 11, 2005) for reasons of record set forth in the Office Action mailed October 11, 2005 and May 22, 2006.

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that the subject matter taught by Idusogie et al. was not included in its provisional application USSN 60/080,447; specifically, applicant asserts that Idusogie et al. teach Fc variant antibody comprising amino acid substitution at position 270, 322, 329, and 331; as such, applicant asserts that Idusogie et al. do not anticipate the claimed invention.

This is not found persuasive for following reasons:

Contrary to applicant's reliance on the claims in the prior art patent, it is noted that under 35 U.S.C. 102(e), the entire disclosure of a U.S. patent, a U.S. patent application publication, or an international application publication having an earlier effective U.S. filing date (which will include certain international filing dates) can be relied on to reject the claims. See MPEP 2136.02.

Here, Idusogie et al. teach treatment method using antibodies variant (e.g. anti-CD20 antibody see column 40, in particular) comprising amino acid substitutions in the Fc regions, e.g. position 334; such variants can binds Fc receptors but does not activate complement (e.g. see entire document, particularly Summary of the Invention on columns 4-5 and columns 18-20). The 334 variant is supported by the disclosure in the provisional application USSN 60/080,447 (e.g. see page 53 of the USSN 60/080,447). Regarding the claimed limitation of "mediates ADCC more effectively", given that methods of treatment taught by Idusogie et al. are administering the same anti-CD20 antibody comprising the same amino acid substitution in the Fc region, it would be inherent properties of the prior art anti-CD20 variant antibody to be able to "mediate ADCC more effectively" than the unmodified antibody.

Applicant further argues that Idusogie et al. teach that the K334 mutant does not activate complement; thus, applicant argues that one skill in the art would not have used K334A mutant.

This is not found convincing for following reasons:

Contrary to applicant's assertions that one skill in the art would not have used the K334 mutant because it is not able to activate complement, it is noted the arguments of counsel cannot take the place of objective evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(c).

In this case, applicant has not provide objective evidence to show why one skill in the art would not have used the antibody variant comprising K334 mutant, given that Isudogie et al. clearly teaches that the antibody variant can be administered to human to treat diseases (e.g. see in vivo uses for the polypeptide variant in columns 34-36). Given that the reference teaches every claimed element of the instant application and the public is in possession of the claimed method before the date of the invention, the reference teachings anticipate the claimed invention.

Thus, applicant's arguments have not been found persuasive.

See Office Action mailed October 11, 2005 and May 22, 2006 for detailed analysis.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is 571-272-8142. The examiner can normally be reached on 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Chun Crowder
Patent Examiner
June 18, 2007

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PRIMARY EXAMINER
TC 1600
6/21/07